Paraoxonase 1 (PON1), agricultural organophosphate exposure, and Parkinson disease

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Abstract

Background—Human, animal and cell models support a role for pesticides in the etiology of Parkinson disease. Susceptibility to pesticides may be modified by genetic variants of xenobiotic enzymes, such as paraoxonase, that play a role in metabolizing some organophosphates.

Methods—We examined associations between Parkinson disease and the organophosphates diazinon, chlorpyrifos, and parathion, and the influence of a functional polymorphism at position 55 in the coding region of the *PON1* gene (PON1-55). From 1 January 2001 through 1 January 2008, we recruited 351 incident cases and 363 controls from three rural California counties in a population-based case-control study. Participants provided a DNA sample, and residential exposure to organophosphates was determined from pesticide usage reports and a geographic information system (GIS) approach. We assessed the main effects of both genes and pesticides in unconditional logistic regression analyses, and evaluated the effect of carrying a PON1-55 MM variant on estimates of effects for diazinon, chlorpyrifos, and parathion exposures.

Results—Carriers of the variant MM *PON1*-55 genotype exposed to organophosphates exhibited a greater than 2-fold increase in Parkinson disease risk compared with persons who had the wildtype or heterozygous genotype and no exposure (for diazinon, odds ratio = 2.2 [95% confidence interval = 1.1–4.5]; for chlorpyrifos, 2.6 [1.3–5.4]). The effect estimate for chlorpyrifos, was more pronounced in younger-onset cases and controls (≤60 years) (5.3 [1.7–16]). No increase in risk was noted for parathion.

Conclusion—The increase in risk we observed among PON1-55 variant carriers for specific organophosphates metabolized by PON1 underscores the importance of considering susceptibility factors when studying environmental exposures in Parkinson disease.

The etiology of Parkinson disease, as with many complex diseases, is widely believed to be multi-factorial, i.e., involving environmental and genetic risk factors. One notable and widely acknowledged environmental risk factor of etiologic importance for Parkinson disease is exposure to pesticides.[1] Organophosphates, a group of pesticides commonly used

in agriculture, are recognized neurotoxins and have been implicated in some studies of Parkinson disease.[2,3] It has also been suggested that susceptibility to the adverse effects of neurotoxins might be modified by genes encoding for possible functional variants of xenobiotic metabolizing enzymes. Paraoxonase, the product of the *PON1* gene, has been shown to determine an individual's susceptibility to organophosphates, especially the insecticides diazinon and chlorpyrifos, such that individuals with low PON1 activity might be at higher risk for adverse health effects from organophosphate exposure.[4] Studies report that the oxygen analogs of chlorpyrifos and diazinon (but not parathion) are efficiently degraded in vivo by paraoxonase.[5,6] While these studies provide evidence that paraoxon, the oxygen analogue of the parathion responsible for the enzyme's name, may in fact not be efficiently degraded by PON1, we nevertheless include this organophosphate to further investigate these novel findings.

We conducted a case-control study of Parkinson disease in a rural population of California's Central Valley among people living close to areas with extensive agricultural pesticide application, especially organophosphate applications. We developed a novel method of estimating pesticide exposure using a geographic information system (GIS) tool and data from California Pesticide Use Reports, land-use maps, and geocoded residential historical locations to assess residential exposures to agricultural organophosphate applications. Here we examine associations between Parkinson disease and environmental exposure to the organophosphates diazinon, chlorpyrifos, and parathion, and we investigate whether a functional polymorphism at position 55 in the coding region of the *PON1* gene (PON1-55) modifies these associations.

Methods

Study design

This study was conducted as part of the UCLA (Parkinson's Environment and Genes Study, a population based case-control study that recruited incident cases and controls from three rural California counties (Fresno, Tulare, Kern) between 1 January 2001 and 1 January 2008. Cases were recruited from local neurologists, through large medical groups, and by public service announcements. Of the 1,167 cases who were initially invited, 563 were eligible to participate in the study. Eligibility criteria included having received a first Parkinson disease diagnosis no longer than 3 years prior to recruitment and being sufficiently healthy to be examined; currently residing in one of the three counties; and residing in California for at least 5 years prior to recruitment. A total of 473 (84%) eligible cases were examined by a UCLA movement disorder specialist and confirmed as having clinically "probable" or "possible" Parkinson disease.[7] The remaining 90 potential cases could not be examined or interviewed (46 [51%] withdrew, 27 [30%] were too ill or died, and 17 [19%] moved out of the area before the exam or did not attend their scheduled appointment); 96 patients were examined but excluded due to diagnoses other than idiopathic Parkinson disease. Of the remaining 377 cases, 9 cases did not provide all necessary demographic information; we were unable to estimate pesticide exposures for 12 cases; 4 cases did not provide a DNA sample; and the DNA sample failed during genotyping for 1 case—leaving 351 cases.

Controls from the same tri-county area were identified through a random sample of Medicare enrollees and from homes identified at random from tax assessor housing unit data listed on residential parcel maps. A residential parcel map contains information on properties and their location, including identification numbers, lot dimensions, streets, and street names. A total of 1,297 potential controls were contacted for eligibility by mail and phone. Eligibility criteria included (1) not having Parkinson disease; (2) being at least 35 years of age; (3) current residency in one of the counties of interest; (4) residing in

California for at least 5 years prior to recruitment, and (5) not being too ill to participate in our study. For parcel controls, only one person per parcel unit was allowed to enroll. Of the 822 eligible population controls, 414 controls did not participate (declined, or moved out of the tri-county area prior to interview); 5 controls did not provide adequate demographic information for this analysis; we were unable to derive pesticide exposure estimates for 15 controls; 24 controls did not provide a DNA sample for genotyping; and 1 control's DNA sample failed during genotyping—leaving us with 363 controls.

Exposure assessment

Each study participant completed a telephone interview with questions on demographic and lifestyle characteristics and a detailed lifetime residential history. Residential pesticide exposure was estimated for each study participant using their residential history and a GIS-based system, which combined pesticide use reporting data and land use maps.[8,9] Pesticide use records provide information on the location and date of an application, the active ingredient, poundage applied, application method, the crop type and acreage of the field. We calculated a time-specific average exposure estimate for each subject. Specifically, we summed pounds of pesticide per year applied within a 500-meter radius buffer of each residence (as suggested by previous literature[10–12]) and weighted this by the proportion of acreage treated within the buffer. For each subject we calculated the period-specific average of all pesticide applications separately for diazinon, chlorpyrifos, parathion, and the group of all other organophosphates (n = 64) applied in California agriculture between 1974 and 1999.

Occupational pesticide exposure estimates were based on both a lifetime history of occupational titles and self-reports of agricultural pesticide applications, as well as information pertaining to specific job tasks involving pesticide exposure. Based on this information, study participants were considered not exposed, possibly exposed (including individuals involved in grading, sorting, packing, or office-related work in the agricultural sector), or likely exposed (including involvement in general farmwork, ground maintenance work, or pesticide application) to pesticides in their occupations.

All study participants provided written informed consent and the study was approved by the UCLA Institutional Review Board.

Genotyping methods

DNA extraction and genotyping for *PON1-55(rs854560)* was performed at GenoSeq, the UCLA Genotyping and Sequencing Core Facility, using whole blood or buccal cell samples. We followed polymerase-chain-reaction conditions described in Akhmedova *et al,* [13] using forward primer 5′-BIO TGGATCCACATCCTGCAATA-3′ and reverse primer 5′ TTGAAAGTGGGCATGGGTAT-3′. Genotyping was performed using pyrosequencing technology.

Statistical Methods

We assessed Hardy-Weinberg equilibrium for *PON1*-55 in controls using a chi-square test. We compared genotype frequencies in cases and controls, and relied on a recessive inheritance model, comparing cases and controls carrying two variant alleles to those carrying one or more wildtype alleles. We chose a recessive model because a recent study reported the lowest activity for carriers of the homozygote variant of *PON1-55 (i.e. MM)* in human serum irrespective of the *PON1 -108* and *-192* variants, whereas paraoxonase activity among heterozygotes of *PON1-55* varied with the other aforementioned *PON1* variants.[14] We did not employ a log-additive model because it would have required making additional

assumptions about gene dosing and the biologic nature of the statistically assessed gene-environment interactions.

We used the 1974–1999 average pesticide-specific pounds per acre to categorize study participants as having zero, low, or high residential exposure to each organophosphate. We used the median value of pesticide exposure in controls as a cutpoint between low and high categories. For our primary analyses, we grouped those with low and high exposure (low/high). Some study participants had missing values for the residential pesticide estimates (12 cases, 15 controls), primarily because these people were not living in the tri-county area during the relevant timeframe, or because their address information was incomplete during the entire timeframe. We excluded these persons in our primary analysis, and considered them as unexposed in additional sensitivity analyses.

We assessed the main effects of both genes and pesticides using unconditional logistic regression analyses to calculate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). We calculated joint effect estimates by creating indicator variables representing combinations of the number of risk alleles and pesticide exposure levels, and entering these terms into our logistic regression models. We also assessed multiplicative interaction by introducing an interaction term into our logistic models. We stratified by sex and age at diagnosis (≤ 60, >60 years) in some analyses. For genetic and gene-environment analyses, we performed sensitivity analyses including only white persons.

We adjusted all effect estimates for sex, smoking status (ever/never), age (continuous), education (<12 years, 12 years, > 12 years), county (Fresno, Tulare, and Kern) and race (white, black, Latino, Asian, or Native American). In some analyses, we adjusted for occupational pesticide exposure (not exposed, possibly exposed, or likely exposed) and exposure to all other reported organophosphates (defined as greater than median exposure to three or more organophosphates, excluding diazinon, chlorpyrifos, and parathion, between 1974 and 1999).

Results

The Parkinson's Environment and Genes study population is primarily white (80%), with an average age at Parkinson disease onset of 68 years. More controls than cases completed greater than 12 years of education (adjusted OR=0.53 [95% CI = 0.36–0.76]). Cases and controls had similar frequencies of occupational exposures (for likely exposed vs. not exposed, adjusted OR=1.08 [0.74–1.56]), but cases were more likely to be residentially exposed to organophosphates other than diazinon, chlorpyrifos, and parathion for up to 3 vs. more than 3 organophosphates, adjusted OR=1.48 [1.02–2.15]) (Table 1).

PON1-55 met Hardy-Weinberg expectations in controls (p=0.52). The frequency of the *PON1-55* MM homozygous (but not heterozygous) variant genotype was higher among our cases compared with controls (Table 2). Results in the white subsample were similar to the mixed-ethnicity sample for (heterozygotes, OR = 1.04 [CI = 0.73–1.49]; for homozygotes, 1.58 [0.91–2.74]) (eTable 1, http://links.lww.com). There was little difference in the magnitude of effect estimates between men and women or between people aged ≤ 60 and those >60 years.

Residential diazinon and chlorpyrifos exposures were highly correlated, with 81% of those ever exposed to chlorpyrifos also having been exposed to diazinon, and 70% ever exposed to diazinon also exposed to chlorpyrifos. We observed an association between high but not low levels of diazinon exposure and Parkinson disease (Table 3). Stratifying on age did not show evidence of effect measure modification in our logistic model. Exposure to chlorpyrifos, in both low and high exposure groups, was associated with an increased risk of Parkinson

disease; the association seemed to be stronger among people ≤60 years of age with low or high exposure (for ≤60 years, zero vs. low/high: OR = 2.65 [95% CI = 1.19–5.90]; for >60 years, zero vs. low/high: OR = 1.43 [0.98–2.11]). We saw no increased risk of Parkinson disease for people exposed to parathion. Results for all three pesticides were similar for men and women, for white persons only (Table 2, http://links.lww.com), and when adjusting for occupational pesticide exposures.

When examining joint effects of *PON1-55* and organophosphate exposure, we found a 2-fold risk for diazinon-exposed carriers of the MM genotype, compared with persons with the wildtype or heterozygous genotype and no diazinon exposure (OR=2.24 [1.12–4.48]) (Table 4). This risk increase was evident among white people alone (2.68 [1.23–5.83]), even when adjusting in the model for other organophosphates (2.43 [1.04–5.15]) (eTable 3, http://links.lww.com). Those who were exposed to any diazinon but did not carry the homozygous variant genotype exhibited little to no increased risk of Parkinson disease (1.18[0.83–1.68]; among white only, 1.18[0.80–1.75]). For those highly exposed to diazinon, we noticed an even larger increase in risk for MM carriers (zero/low versus high: OR=5.30 [1.71, 16.4]), and strong interaction on the multiplicative scale (OR$_{interaction}$=4.59 [95% CI = 1.37–15.4]) (eTable 4, http://links.lww.com). The association became even stronger when we restricted to white people only, but these results were based on a very small number of highly exposed (zero/low versus high: OR=9.1 [2.0– 41]) (eTable 4). Effect estimates were similar for those ≤60 and >60 years.

Carrying the MM genotype and having been exposed to chlorpyrifos increased the risk of Parkinson disease nearly three times compared to unexposed wildtype/heterozygous *PON1-55* carriers (2.61[1.25–5.44]; white only, 2.95 [1.31–6.64]). The effect estimate was only slightly reduced when we adjusted for exposure to other organophosphates (among whites, 2.67 [1.16–6.15]). Those who were exposed to chlorpyrifos but did not carry the homozygous variant genotype experienced a moderate increase in Parkinson disease risk (All, 1.48 [1.04–2.12]; whites only, 1.48 [1.00–2.17]). In the younger age group (≤60) we again noted an even stronger association for chlorpyrifos-exposed MM genotype carriers (≤60 years, unadjusted OR=5.30 [1.71–16.4] and OR adjusted for all other organophosphates = 6.14 [1.34–28.05]; >60 years, adjusted OR=2.36; [0.97–5.79]).

We did not find any associations between parathion and Parkinson disease, even for exposed *PON1-55* MM genotype carriers in either our mixed ethnicity or whites-only samples (Table 4). Results for pesticide main effect and interaction analyses did not change notably when we included those with missing pesticide exposure information as unexposed (data not shown).

Discussion

Our population-based case-control study was conducted in California's rural Central Valley, an area with substantial agricultural pesticide use. Our results suggest an increased risk of Parkinson disease in study participants exposed to the organophosphates diazinon or chlorpyrifos when they are carriers of a common genetic variant in *PON1*. Both compounds and their oxygen analogs (oxons) are metabolic substrates of the enzyme paroxynase 1.[15] Among study participants exposed to either of these organophosphates, carriers of the variant MM genotype exhibited a greater-than-2-fold risk of Parkinson disease compared with those having the wildtype or heterozygous genotype and no exposure. The risk was even more pronounced for those with high exposure to diazinon and in younger-onset cases (≤60 years) exposed to chlorpyrifos; the latter would have been children or young adults at the time of residential exposure. For the organophosphate parathion, whose oxygen analogue paraoxon is the most well-known metabolic substrate of paraoxonase 1, we did not observe

either a main association or a statistical interaction with *PON1*. Recent data suggests that paraoxon may not be efficiently detoxified by paraoxonase 1 in vivo and thus paraoxonase 1 may not provide protection against paraoxon toxicity.[5]

Our findings are generally in accord with the few previous studies that have examined the relationship of the *PON1*-55 variant and pesticide exposure with Parkinson disease.[16,17] One study examined occupational and hobby pesticide exposures using a job-exposure-matrix approach.[16] While results suggested an interaction, they were based on only a small number of exposed persons and thus did not reach customary significance levels ($OR_{interaction} = 4.43[95\% \ CI = 0.88–22.3]$). A study conducted in Taiwan by Fong *et al*[17] reported an association between Parkinson disease and exposure to pesticides but noted no differences in *PON1* genotype distribution between cases and controls in those who reported pesticide exposures. However, this Taiwanese study[17] included only two persons (1 case, 1 control) with the MM genotype, as the M allele seems to occur at lower frequency in Asian populations.[18] More generally, a genetic susceptibility to organophosphates was suggested by a decade-old case study reporting that three first-degree relatives (mother, her sister, her daughter) all developed symptoms of parkinsonism shortly after staying in a residence fumigated with organophosphates, whereas other exposed relatives residing in the apartment (husband, son, daughter-in law, and grandchildren) did not develop symptoms.[19]

Numerous studies to date have examined and documented associations between pesticide exposure and Parkinson disease, including a meta-analysis[1] and experimental studies conducted in animals and cells, [20–22] but few have considered genetic susceptibility in addition to exposures.[23] Moreover, very few studies to date have evaluated specific pesticides or pesticide classes, and most of these studies have been limited by relying solely on recall, by small sample size, or by inconsistent study findings regarding the specific type of pesticide implicated in the results.[2,3,24,25] For example, while Firestone et al [24] found a large increase in risk of Parkinson disease among parathion-exposed study participants ($OR = 8.1[95\% \ CI = 0.92–71]$; number exposed = 6) but not diazinon ($1.04[0.35–3.1]$; number exposed = 15), Kamel et al [25] noted no associations for organophosphate pesticides, including chlorpyrifos ($0.9[95\% \ CI = 0.5–1.6]$), diazinon ($0.9[0.5–1.7]$), and parathion ($1.1[0.6–2.2]$). On the other hand, a German case-control study[3] found participants with repeated exposure to particular classes of pesticides, organochlorines or alkylated phosphates and carbamates to be at increased risk of developing Parkinson disease. Our findings are further supported by a recent family-based study[2] that found applications of pesticide in the organochlorine and organophosphate classes of chemicals (as reported by study participants) to moderately increase their risk of Parkinson disease (by 50%). Published case study reports have also described incidences of extrapyramidal parkinsonism as a complication of acute poisoning by organophosphates. [19,26–28]

It is important to assess whether organophosphates play an etiologic role in Parkinson disease because chlorpyrifos and diazinon (both of the subclassifications of phosphorothionates) are ranked among the top 20 potential toxic air contaminants by the California Department of Pesticide Regulation.[29] A California health risk evaluation[29] conducted in California's Central Valley between 1986 and 2000 found that the organophosphates chlorpyrifos and diazinon ranked high in acute inhalation toxicity (after only three other fumigants with higher vapor pressures). After being applied for agricultural purposes, chlorpyrifos, diazinon, and other organophosphates can travel through air by spray drift and post-application volatilization, and can persist in the environment. Their half lives on foliage are just a few days, but in the soil they can last much longer (up to 1575 days for chlorpyrifos and 87 days for diazinon).[30] Additionally, pesticides applied outdoors may be brought into homes by humans and pets, where they can persist for months or years. Typically, pesticide concentrations in indoor air and house dust are 10–100 times those

found in outdoor air and surface soil.[31] Furthermore, animal and human studies suggest that even moderate doses of organophosphates, including chlorpyrifos, are neurodevelopmental toxicants, i.e. the developing nervous system is more highly susceptible to their effects.[32,33] Children may receive greater exposure relative to their body size because they breathe more air per unit of body weight, engage in extensive hand-to-mouth contact, and are closer to the floor where pesticides may settle.[32] These observations may in part explain the more pronounced effect estimates we observed for younger-onset cases (≤60 years), who may have been children or young adults at their earliest time of chlorpyrifos exposure.

Organophosphates exert their toxic effects by inhibiting the activity of acetylcholinesterase at nerve endings, leading to the accumulation of the neurotransmitter acetylcholine, and affecting the parasympathetic, sympathetic, motor, and central nervous systems.[34] In the ambient air, organophosphate phosphorothionates degrade by reacting with hydroxyl radicals to form oxon compounds. These oxon compounds are more reactive and are stronger inhibitors of acetylcholinesterase than are their parent compounds.[30] Organophosphates are generally highly lipid soluble and can be absorbed upon exposure by the skin, mucous membranes, gastrointestinal system, and respiratory system.[34]

The protein encoded by *PON1* is a high-density lipoprotein (HDL)-associated esterase, and is key in detoxifying organophosphorous compounds including the oxygen analogs of chlorpyrifos and diazinon.[15] Five *PON1* promoter region polymorphisms and two *PON1* coding region polymorphisms (including *PON1*-55) have been identified.[4] However, two recent studies found that haplotype information for the 5 most common SNPs (three in the promoter region and the two coding region SNPs L55M and Q192R) only marginally strengthened the genotype-phenotype relationship for PON1 enzymatic activity.[35,36] In this study, we focused on the position 55 polymorphism because previous studies conducted in white populations noted an association between this polymorphism and Parkinson disease. [13,37] Studies of *PON1* Q192R or T108C variants, however, found no associations with Parkinson disease in white populations.[38–40] Although variation in *PON1*-55 has been shown to not affect catalytic efficiency,[15,41] the M allele of *PON1*-55 has been associated with lower levels of PON1 activity, of circulating PON1, and of PON1 mRNA.[15,42–43] In fact, a recent study[14] reported a much lower mean activity towards diazoxon in human serum under physiologic conditions for the 55MM genotype compared with the LM and the LL genotypes, irrespective of the *T(-108)C* and *Q192R* variants. This may be due to well-demonstrated and strong linkage disequilibrium with various promoter region polymorphisms that determine low *PON1* expression.[15] It has also been postulated that protein stability or association of paraoxonase 1 with HDL could be affected by the position 55 polymorphism.[44] Thus, as is the case with all genetic association studies, we cannot attribute our findings to the *PON1*-55 allele, nor can we be sure that our findings are a result of low PON1 activity. Our approach of using the *PON1*-55 genotype is limited, compared with a two-dimensional enzyme analysis[45] that would assess an individual's serum PON1 activity. However, such analysis was not feasible in our study. Additionally, environmental factors such as smoking have been shown to modulate paraoxonase 1 levels and activity in the short term[46]; thus we adjusted for smoking in all analyses. Lastly, although we performed sensitivity analyses restricted to whites only, we cannot rule out the possibility of population stratification within ethnic groups.

A large percentage of our study participants were exposed to organophosphate pesticides through close residential proximity to areas of extensive agricultural pesticide applications. Our GIS approach builds on pesticide use reports collected over decades in California. This allowed us to estimate exposures for specific pesticides and avoid problems of poor subject recall for historical and specific pesticide exposures. Our exposure measures are still likely to have suffered from misclassification – albeit non-differential misclassification—due to

incomplete address information and geocoding difficulties, differences in wind patterns during or after pesticide applications, amount of time spent at home, and introduction of pesticides into the home. Additionally, the relatively low response rate among controls raises concern about selection bias. Factors that influence participation and are related to both disease status and environmental exposures to pesticides could bias main pesticide effect estimates; these are less likely to be related to *PON1* genotype. Under the assumption that genotype does not influence participation conditional on exposure and disease, the gene-environment interaction estimates should not be affected, even if selection is jointly influenced by exposures and disease, and whether the genotype is related to exposure, disease, or both.[47] Lastly, although our findings point to specific and plausible pesticide-gene interactions, there is a plethora of pesticides applied in agriculture. Adjustment for a summary measure of other organophosphates and occupational pesticide exposures did little to change our results.

Our study is distinguished from previous studies by our reliance on recorded pesticide use data coupled with a GIS approach, and by our focus on *PON1*-55 as it relates to specific organophosphates. Our finding of an increased risk of Parkinson disease in subjects exposed to specific organophosphates among *PON1*-55 variant carriers compared with unexposed wildtype or heterozygote carriers underscores the importance of considering functional genetic variants of xenobiotic metabolizing enzymes when studying the influence of environmental exposures on Parkinson disease risk. If there are vulnerable subpopulations with increased genetic susceptibility to environmental toxins, efforts may be needed to protect such groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of Study Population

	Cases (No. = 351) (%)	Controls (No. = 363) (%)
Sex (Male); no. (%)	199 (57)	179 (49)
Age		
Median (SD)	70.0 (10.4)	69.0 (12.4)
Distribution; no. (%)		
≤60 years	77 (22)	103 (28)
>60 years	274 (78)	260 (972)
Race		
White	282 (80)	290 (80)
Black	3 (1)	14 (4)
Latino	46 (13)	32 (9)
Asian	4 (1)	11 (3)
Native American	16 (5)	16 (4)
County		
Fresno	159 (45)	142 (39)
Kern	122 (35)	142 (39)
Tulare	70 (20)	79 (22)
Education		
0 to <12 years	64 (18)	37 (10)
12 years	97 (28)	73 (20)
>12 years	190 (54)	253 (70)
Cigarette Smoking		
Never	186 (53)	162 (45)
Current	21 (6)	33 (9)
Former	144 (41)	168 (46)
Occupational Pesticide Exposure[a]		
Not exposed	213(61)	239 (66)
Maybe exposed	22 (6)	24 (7)
Likely exposed	116 (33)	100(28)
Organophosphate Exposure[b]		
0 to <3 organophosphates	238(68)	275(76)
≥3 organophosphates	113 (32)	88 (24)

[a] JEM classification of pesticide exposure based on occupational codes and self-reported agricultural and ground maintenance pesticide applications

[b] Greater than median exposure to three or more organophosphates, excluding diazinon, chlorpyrifos, & parathion, between 1974–1999.

Table 2

Association of PON1 Leu-Met 55 Genotype Frequencies with Parkinson disease

	Cases (n=351) No. (%)	Controls (n=363) No. (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
PON1-55				
LL[b]	159 (45)	180 (50)	1.00	1.00
LM	144 (41)	148 (41)	1.10 (0.81–1.51)	1.04 (0.75–1.44)
MM	48 (14)	35 (10)	1.55 (0.96–2.52)	1.45 (0.87–2.40)
LL+LM[b]	303 (86)	328 (90)	1.00	1.00
MM	48 (14)	35 (10)	1.49 (0.94–2.36)	1.43 (0.88–2.30)

[a] Adjusted for age (continuous), sex, ever-smoked, race, county, education (school years)

[b] Reference category

Table 3

Association of Residential Exposure to Chloropyrifos, Diazinon, Parathion with Parkinson Disease

	Cases (n=351) No. (%)	Controls (n=363) No. (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Diazinon				
Zero[b]	149 (43)	184(51)	1.00	1.00
Low	77 (22)	90(25)	1.06 (0.73–1.53)	1.02 (0.68–1.53)
High	125 (37)	89(25)	1.73 (1.23–2.45)	1.55 (1.05–2.30)
Chloropyrifos				
Zero[b]	170 (48)	215(59)	1.00	1.00
Low	93 (27)	74(20)	1.59 (1.10–2.29)	1.56 (1.06–2.31)
High	88 (25)	74(20)	1.50 (1.04–2.18)	1.56 (1.02–2.40)
Parathion				
Zero[b]	185 (53)	198(55)	1.00	1.00
Low	76 (22)	82(23)	0.99 (0.69–1.44)	0.82 (0.54–1.21)
High	90 (26)	83(23)	1.16 (0.81–1.66)	0.98 (0.65–1.48)

[a] Adjusted for age (continuous), sex, ever-smoked, race, county, education (school years)

[b] Reference category

Table 4

Interaction between PON1 Leu-Met 55 and Diazinon, Chlorpyrifos, and Parathion exposure in association with Parkinson Disease

	Zero Exposure			Low/High Exposure		
	No. Cases/Controls	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	No. Cases/Controls	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Diazinon						
PON1-55						
LL+LM	133/164	1.00[b]	1.00[b]	170/164	1.28 (0.93–1.75)	1.18 (0.83–1.68)
MM	16/20	0.99 (0.49–1.98)	1.00 (0.49–2.04)	32/15	2.63 (1.37–5.06)	2.24 (1.12–4.48)
OR (95%) for Interaction					2.67 (1.09–6.55)	2.23 (0.89–5.62)
Chloropyrifos						
PON1-55						
LL+LM	149/193	1.00[b]	1.00[b]	154/135	1.48 (1.08–2.02)	1.48 (1.04–2.12)
MM	21/22	1.24 (0.66–2.33)	1.17 (0.61–2.25)	27/13	2.69 (1.34–5.39)	2.61 (1.25–5.44)
OR (95%) for Interaction					2.18 (0.89–5.31)	2.01 (0.80–5.01)
Parathion						
PON1-55						
LL+LM	157/177	1.00[b]	1.00[b]	146/151	1.09 (0.80–1.49)	0.90 (0.64–1.28)
MM	28/21	1.50 (0.82–2.75)	1.47 (0.78–2.75)	20/14	1.61 (0.79–3.30)	1.21 (0.57–2.60)
OR (95%) Interaction					1.07 (0.44–2.60)	0.94 (0.38–2.35)

[a] Adjusted for age (continuous), sex, ever-smoked, race, county, education (school years)

[b] Reference category